United Kingdom

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Introduction

In the UK, clinical trials are regulated by:

(i) The Medicines and Healthcare products Regulatory Agency (MHRA); specifically, the Clinical Trials Unit of the Licensing Division of the MHRA; and

(ii) Research Ethics Committees (REC's), which have been established and operate in accordance with the standards and guidelines set out in the UK's Research Ethics Framework.

Regulatory Framework

UK Regulatory Framework

The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended (the UK Regulations) implement Directive 2001/20/EC (the Directive) on good practice in the conduct of clinical trials on medicinal products for human use.

The Directive and the UK Regulations cover all investigations and studies undertaken to ascertain the efficacy or safety of a medicinal product in human subjects but do not cover non-interventional trials.

Trials Involving Higher-Risk IMPs

As a result of the subjects in the first-in-man trial of the anti-CD28 monoclonal antibody TGN1412 in 2006 suffering catastrophic systemic organ failure, the UK government subsequently established the Expert Scientific Group (ESG) to consider the transition from pre- clinical to first-in-man phase 1 trials, and the design of these trials, with specific reference to the following investigational medicinal products (IMPs):

- Biological molecules with novel mechanisms of action;
- New agents with a high degree of species specificity; and
- New agents with immune system targets.

In December 2006, the ESG report *Expert Group on Phase One Clinical Trials* was published. The report sets out certain recommendations, including expediting the collection of information from such unpublished studies relevant to the safety of human exposure, taking a broad approach to dose calculation (the Minimal Anticipated Biological Effect Level (MABEL) approach is recommended as a model for achieving this), building in a safety margin when calculating starting doses in man, carefully considering the route and rate of administration of first doses, administering new agents (and escalating doses thereof) in first-in-man trials sequentially with appropriate periods of observation in between, carefully justifying whether to conduct a first-in-man trial in healthy volunteers or in volunteer patients, using principal investigators appropriately knowledgeable to make informed clinical judgments in such trials, considering a treatment strategy in studies where there is a predictable risk of certain types of severe adverse reaction, conducting such studies in an appropriate clinical environment with immediate access to acute emergency facilities and pre-arranged access to intensive care facilities in reasonable proximity, and informing trial subjects of what to do should they experience symptoms of an adverse reaction.

As detailed below, the sponsor of a clinical trial involving an IMP must submit a Clinical Trial Authorization (CTA) application to the MHRA. However, the MHRA regards certain IMPs as posing higher risks, namely those IMPs that:

- May act directly or indirectly on the immune system via a novel target or a novel mechanism of action;
- May have the potential for a secondary effect on the immune system via a mechanism that is not well characterized; and
- May act via a species-specific mechanism or have an activity that is unlikely to be predicted through animal studies.

The MHRA reviews trials involving higher-risk IMPs differently from trials of other IMPs; they seek advice for first-in-man trials of higher- risk IMPs from the Expert Advisory Group of the Commission on Human Medicines before approval can be given. If sponsors are in doubt as to whether their IMP is viewed as higher-risk, they can submit a summary of the nature of the IMP, its target or mechanism of action, and the relevance of the animal model(s), to the MHRA for guidance.

Clinical Trial Authorizations (CTAs)

Under the UK Regulations, no person may:

- Conduct or start a clinical trial or cause such a clinical trial to be started;
- Recruit, or advertise recruitment for, a clinical trial; or
- Sell or supply IMPs to certain individuals for use in a clinical trial,

unless the proposed clinical trial has received:

- A favorable opinion from the relevant REC; and
- A CTA from the MHRA.

Where the clinical trial is to be undertaken within the National Health Service (NHS), approval must be sought from each NHS organization involved. Such consent is termed 'NHS permission for research', but is often described as 'R&D approval'.

Depending on the type of IMP and the nature of the proposed clinical trial, it may also be necessary to obtain approval from other bodies.

For example, approval from the UK's Department for Environment, Food and Rural Affairs must be obtained for a trial involving genetically modified organisms for contained use activities, the Administration of Radioactive Substances Advisory Committee for trials involving radioactive substances, and the clinical investigations unit of the MHRA for trials involving medical devices.

CTA Application

Before the CTA application may be submitted to the MHRA, the sponsor should obtain a unique EudraCT number from the EudraCT database. This number will identify the protocol for a trial whether conducted at a single site or at multiple sites in one or more member states.

A CTA application consists of:

(i) Covering letter containing the EudraCT number for the trial and the sponsor protocol number with a title of the trial. The letter should draw attention to any special issues related to the application such as special trial populations, first administration of a new active substance to humans, and unusual IMPs. The letter should also refer to any scientific advice related to the trial or IMP given by the European Medicines Agency or the competent authority of any other country that has been provided, and if so, indicate where in the application this can be found. If the application is being made by anyone other than the sponsor, an additional covering letter must be included from the sponsor, authorizing the applicant to act on its behalf.

(ii) Completed CTA application form setting out all the key details of the proposed trial including the organizations and key individuals to be responsible for the conduct of the trial.

(iii) Protocol, which must comply with Good Clinical Practice (GCP) guidelines. The protocol must define the end of the proposed trial, be clearly referenced to ensure clarity in the event of subsequent amendments and variations and be signed by the sponsor and principal investigator (or coordinating investigator for multicenter trials). The protocol should also include:

- An evaluation of the anticipated benefits and risks as indicated in the Directive;
- A justification for including subjects who are incapable of giving informed consent or other special populations, as applicable; and
- A description of the plan for the provision of any additional care of the trial subjects once their participation in the trial has ended, where it differs from what would normally be expected for those subjects' medical condition(s), as applicable.

(iv) Investigator's brochure as prepared from all available information and evidence that supports the rationale for the proposed clinical trial and the safe use of the IMP in the trial. The investigator's brochure should be presented in the form of summaries. If the IMP and the proposed use of the IMP have been authorized in any Member State, the approved Summary of Product Characteristics (SmPC) will replace the investigator's brochure. Where the proposed conditions of use in the trial differ from those authorized, the SmPC should be complemented with a summary of relevant non-clinical and clinical data supporting the proposed new use of the IMP in the trial.

(v) Complex IMP-related data and information are required to support the quality of the IMP including in relation to the manufacture and control of the IMP, non-clinical studies and from its clinical use. Guidance is published by both the MHRA and the European Commission regarding the requirements with regard to this data.

(vi) XML file of the application form (complete data set).

(vii) Applicable fee payable to the MHRA.

Please see above for details of the more rigorous review process undertaken for CTA applications for trials involving higher-risk IMPs.

Sponsor and Contract Research Organizations (CROs)

Sponsors' Responsibilities

Under the UK Regulations, 'sponsor' means, in relation to a clinical trial, the person who takes responsibility for the initiation, management and financing (or arranging the financing) of that trial. Thus, a sponsor's ultimate responsibilities include:

- Obtaining the CTA from the MHRA;
- Obtaining approvals from any other bodies, where relevant;
- Making the necessary arrangements to conduct the trial in accordance with the principles of GCP;
- Complying with the requirements to report serious unexpected adverse reactions (SUSAR's) to the MHRA and relevant REC within the required time limits;
- Providing the MHRA and relevant REC with an annual safety report;
- Permitting any trial premises to be inspected by the MHRA as required;
- Paying the MHRA's Annual Service Fee;
- If a trial is terminated before its planned conclusion, notifying the MHRA and REC within 15 days of the trial termination;
- Submitting the appropriate EudraCT form declaring the end of the trial to the MHRA within 90 days of the trial conclusion; and
- Subsequently submitting an end of trial study report to the MHRA within one year of the trial conclusion.

The UK Regulations allow a partnership or group between them to fulfill this sponsorship responsibility. Under this approach, which is common for publicly funded trials, the applicant for a CTA can either accept all of the sponsor's responsibilities or notify the MHRA that its partners accept responsibility for some functions.

Under the UK Regulations, a sponsor must either be established in a state within the European Economic Area (EEA), or else have a legal representative who is so established. Legal representatives take the position of the sponsor with regard to civil and criminal liability; where there is no sponsor present in the EEA, a legal representative acquires the civil and criminal liability of the sponsor in accordance with the Directive.

Sponsors may delegate any or all of their trial-related tasks, duties and functions to individuals, companies, institutions or organizations, including CROs.

However, in such cases where the sponsor delegates any or all of its responsibilities under a trial to, for instance, a CRO:

- There must still be an overall sponsor for the trial; and
- The sponsor remains ultimately responsible for ensuring that the conduct of the trials and the final data generated by those trials comply with the requirements of the Directive.

Because the sponsor retains ultimate responsibility for the trial, it is up to the sponsor to ensure that any CRO or other organization to which it delegates will fulfill its responsibilities in relation to the trial in accordance with the UK Regulations including, for instance, the principles of GCP. The MHRA is willing to inspect trial-related premises,

including those belonging to CROs, to check for GCP compliance and to provide sponsors with general advice in relation to issues such as delegation. All trial-related responsibilities should be defined, established and allocated prior to the trial being initiated.

Trials initiated or sponsored by authorized health professionals are permitted in the UK. The medical professionals involved in these trials tend to work in the UK's National Health Service, university research laboratories or within charitable organizations such as Cancer Research UK.

The actual means of funding such trials or any trial is not prescribed by the UK Regulations. The researcher's own employer may, however, impose certain funding restrictions or requirements and these would need to be investigated. The aim of the UK Regulations is to permit flexibility in the funding of clinical trials and the UK Regulations do not specifically prohibit pharmaceutical companies from funding such trials in whole or in part.

The UK Regulations do, however, require disclosure of all trial funding measures to, and approval of them by, an REC as part of the process of obtaining a favorable REC opinion (necessary for all trials, as detailed above). Any conditions attached by a funder to their offer of funding (including those by a pharmaceutical company) would

need to be disclosed and validated by the REC.

Clinical Trial Agreements

Clinical trial agreements are not necessarily subject to review by the MHRA or the relevant REC responsible for assessing the trial. However, certain aspects of the trial proposals are subject to review (e.g., arrangements regarding trial financing, access to source data and records, etc.), and in practice, clinical trial agreements may be appended to the trial protocol, which is subject to review by both the MHRA and the REC at the point of application for CTA and ethical approval.

The Investigator

The UK Regulations define 'chief investigator' and 'investigator'. Chief investigator means, for a single site trial, the investigator for that site and, for a multiple-site trial, the authorized health professional who takes primary responsibility for the conduct of the trial (irrespective of whether he/she is an investigator at a particular trial site). Each trial site must have an investigator. The investigator is the authorized health professional for the conduct of the trial at a particular trial site.

The UK Regulations impose obligations on the chief investigator and investigator.

Responsibilities of Chief Investigator

One of the main responsibilities of the chief investigator during the approval process for a clinical trial is to apply for and obtain an opinion from a relevant REC which is favorable and supports the conduct of the clinical trial. As stated above, a clinical trial cannot proceed without such an opinion. The application for an REC opinion is governed by UK Regulation 14.

The application must be made in writing in English, signed by the chief investigator and accompanied by a list of particulars that is too long to repeat here but which is set out in Part 1 of Schedule 3 of the UK Regulations. In the event of an unfavorable opinion of the REC, the chief investigator has responsibility for appealing the decisions where there are grounds for appeal.

Pursuant to UK Regulation 31A, the chief investigator, in addition to the sponsor, must ensure that the contents of the trial master file and the medical files of trial subjects are retained for at least five years after conclusion of the trial and during that period are:

- Readily available for to the MHRA on request; and
- Complete and legible.

Where ownership of these materials vests in the sponsor, the chief investigator may need to agree with the sponsor as to how it will discharge these responsibilities.

Responsibilities of Investigator

Each trial site shall have an investigator who is to be responsible for conducting the trial at that site in accordance with:

(i) The protocol;

(ii) The conditions and principles of GCP;

(iii) The investigator's brochure;

(iv) The IMP dossier; and

(v) Any conditions imposed per the REC opinion.

These responsibilities will include reviewing subject applications, undertaking subject assessment, application of trial qualification criteria, subject intake including obtaining informed consent, administration of IMP and any additional planned or unplanned health care provision at the trial site.

While the above documents will form part of the trial master file, the investigator usually assists the sponsor by enriching the trial master file and creating, maintaining and updating medical files for trial subjects.

As an authorized health professional, the investigator is also required, in the conduct of the trial, to observe the professional duties applicable to his/her profession.

As to pharmacovigilence, an investigator is required, pursuant to UK Regulation 32, to report any SUSAR event which occurs in a subject at a trial site at which he/she is responsible for the conduct of a clinical trial immediately to the sponsor. An immediate report may be made orally or in writing and following the immediate report of such an event, the investigator must make a detailed written report on the event. SUSAR events and adverse events anticipated by the trial protocol or investigator's brochure and stated not to require immediate reporting, must be reported in accordance with the requirements of the protocol.

Where the reported event consists of, or results in, the death of a trial subject, the investigator shall supply:

- The sponsor; and
- In any case where the subject's death has been reported to the relevant REC, that REC,

with any additional information requested by the sponsor or REC respectively.

Study Drugs

Authorizations

The key authorizations that are required to administer the study drug are the CTA from the MHRA and the favorable ethical opinion from the relevant REC.

Financing Arrangements

Under the UK Regulations, the sponsor is required to make the IMP and any devices used to administer the product available free of charge, subject to NHS prescription charges (GBP 7-8 per prescription product).

The cost of a medicinal product used in a clinical trial is not reimbursable under the UK's Prescription Price Regulation Scheme unless or until a marketing authorization exists for it in the UK.

It is up to the sponsor to stipulate in the protocol the financing arrangements for the associated aspects of treatment involved in the clinical trial, including any medical procedures. Theoretically, the sponsor may provide that it will not finance such aspects of treatment. However, in practice this would be extremely unusual for pharmaceutical clinical trials, as generally such treatment would fall outside the scope of the clinical trial and would then be financed by the clinical trial subject's health care provider (whether the NHS or a private health insurer). Even if, for some particular reason, such treatment is outside the scope of the clinical trial, refusal by the sponsor to finance the treatment (or indeed any aspect of the trial) would mean that very few subjects would volunteer to participate in the clinical trial.

Liability

The Directive requires sponsors to provide evidence of insurance cover or to provide an indemnity to cover their potential liabilities to the subjects participating in a clinical trial. Under the UK Regulations, sponsors are not required to take out clinical trials insurance, but the REC providing an opinion on the proposed clinical trial may well seek assurance that adequate insurance cover has been purchased, depending upon its view on the indemnity provided by the sponsor, in relation to the risks posed by the specific trial.

In the UK model clinical trials agreement for use in trials involving the NHS (which the Department of Health, the Association of the British Pharmaceutical Agency (ABPI) and the BioIndustry Association all recommend that these be used routinely without alteration for all clinical trials in the UK), provision is made for the sponsor indemnifying and holding harmless the NHS hospital and its employees and agents from all claims and proceedings brought by or on behalf of clinical trial subjects and the NHS hospital. The model clinical trials agreement provides for certain restrictions and qualifications in regard to the indemnity; the indemnity shall not apply to any claim or proceeding:

(i) To the extent that personal injury (including death) is caused by the negligent or wrongful acts or omissions, failure to comply with the trial protocol or breach of statutory duty, of or by the NHS hospital, its employees or agents;

(ii) Unless, as soon as "reasonably practicable" following receipt of notice of the claim or proceeding, the NHS hospital notifies the sponsor in writing and permits the sponsor to have full care and control of the claim or proceeding (for instance, using legal representation of its own choosing); and

(iii) If the NHS hospital, its employees, or agents have made any admission regarding, or taken any action relating to, such a claim or proceeding, which will be prejudicial to the defense of it, without having first received consent from the sponsor. This does not preclude the NHS hospital following its internal complaint, accident or disciplinary procedures or taking any action as required by law.

Furthermore, the ABPI, which favors an expeditious procedure in relation to compensation for injury caused by participation in clinical trials, has published a set of compensation guidelines that it recommends that all sponsors:

- Incorporate into their clinical trials agreements (the UK model clinical trials agreement incorporates these guidelines); and
- Provide assurance to the investigator and relevant REC that they will adhere to these guidelines in the event of injury being suffered by a trial subject.

Publication

There is ongoing controversy in the UK surrounding the question of whether sponsors should be obliged to publish all (whether positive or negative) results from their trials. The National Research Ethics Service (NRES) advises that RECs are under a lot of pressure to persuade all companies sponsoring trials and who obtain ethical approval, to publish their results, but that they are not yet able to force companies to do so. However, RECs are in a strong position to promote the publication of results, as sponsors' willingness to do so regardless of outcome may influence REC decisions as to whether to approve requests for favorable opinions.

Furthermore, under the Joint Position on the Disclosure of Clinical Trial Information (November 2009), and supported by the ABPI Code, all clinical trials should be registered within 21 days of initiation of patients' enrolment, via the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) clinical trials portal 'Clinical Trial Registries and Databases'.

In addition, applicants for REC approval are also now required to summarize the aim of their research and to allow NRES to publish this (within approximately three months following approval). Theoretically, therefore, the information about a proposed trial may enter the public domain, and thus sponsors may face pressure to publish trial results once available.

Access to Trial Drug Post Trial

It is technically permissible for the sponsor to provide the trial subject with the study drug after the termination of the clinical trial if is properly prescribed (if applicable) and either a valid UK marketing authorization exists for the drug or it can be provided on a named patient basis.

Intellectual Property (IP) and Data

Under English law, the normal principles on intellectual property apply. Unless an agreement vests ownership of intellectual property rights in a party, such ownership shall be held by the person who first created the intellectual property.

In both commercially led and non-commercially led trials, ownership of intellectual property rights in new inventions typically goes with the sponsor, and the sponsor's matrix of agreements supporting the clinical trial usually reflect this outcome.

The sponsor's contract terms, for example, appointing the manufacturer of the IMP, the CRO, the chief investigator, any investigators and other service providers, would typically require ownership of new inventions (including the trial master file or dossier) to vest in the sponsor and require the relevant counterparties to maintain confidentiality.

The matrix of subject consent forms for a trial also typically addresses data protection responsibilities together with custody, sponsor use and trial subjects' access to medical records.

Sometimes an investigator may have an academic interest in publishing research based on trial data. Subject to commercial pressures and the need for the sponsor and its licensors to first perfect intellectual property rights and overriding confidentiality obligations, the sponsor may be in a position to grant investigators publication privileges. These publication rights usually require delayed publication and, frequently, prior approval by the sponsor of the final text of the publication.